

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number
WO 2004/026850 A1

(51) International Patent Classification⁷: C07D 277/82,
317/72, C07C 225/20, A61K 31/429, A61P 25/18, 25/28

(21) International Application Number:
PCT/GB2003/004022

(22) International Filing Date:
17 September 2003 (17.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0221513.5 17 September 2002 (17.09.2002) GB

(71) Applicant (for all designated States except US): GENER-
ICS [UK] LIMITED [GB/GB]; Albany Gate, Darkes
Lane, Potters Bar, Hertfordshire EN6 1AG (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GUPTA, Ashwini,
Kumar [IN/IN]; Type II-B 17, 99-1st Floor, Lake Side
Gate, IIT Bombay Powai, 400 076 Mumbai (IN). AGHAV,
Balu [IN/IN]; c/o Mr. V.N. Deshpande, B-10/1/2/3,
Sector-13, CIDCO Colony, 410 206 New Panvel (E)
(IN). TRIPATHI, Anil, Kumar [IN/IN]; c/o Mr. V.N.

Deshpande, B-10/1/2/3, Sector-13, CIDCO Colony, 410
206 New Panvel (E) (IN). GAITONDE, Abhay [IN/IN];
8, Niwara Co-op Hsg. Soc, Veer Sawarkar Path, Naupade,
400 602 Thane (IN).

(74) Agents: ELENDE, Almut, Susanne et al.; Venner, Shipley
& Co., 20 Little Britain, London EC1A 7DH (GB).

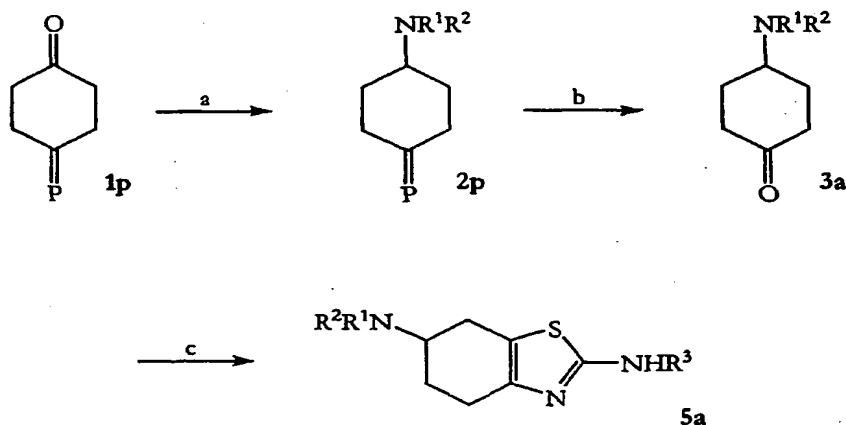
(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF 2-AMINO-4,5,6,7-TETRAHYDRO-6-AMINOBENZOTHIADIAZOLES FROM
CYCLOHEXANES AND CYCLOHEXANONES AS INTERMEDIATES



a: reductive amination with R^1R^2NH
b: deprotection
c: (i) iodine, $H_2N(C=S)NHR^3$; (ii) OH^-

(57) Abstract: The present invention relates to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles (5a) from cyclohexanes (2a) and cyclohexanones (3a) as intermediate.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PROCESS FOR THE PREPARATION OF 2-AMINO-4,5,6,7-TETRAHYDRO-6-AMINO BENZOTHAZOLES
~~FROM CYCLOHEXANES AND CYCLOHEXANONES AS INTERMEDIATES~~

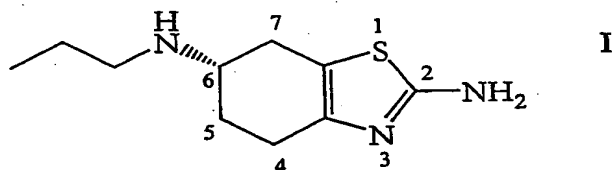
Technical field

- 5 The present invention relates to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles and to novel cyclohexanes and cyclohexanones for use in these processes.

Background art

10

- Certain 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are known to have dopamine D-2 activity and are therefore potentially useful as pharmaceuticals for the treatment of psychiatric disorders such as schizophrenia and Alzheimer's disease. One such compound, the dihydrochloride salt of (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole I (pramipexole), is marketed as a
15 pharmaceutical for the treatment of Parkinson's disease. The numbering of pramipexole I is indicated below.



- 20 Processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are disclosed in patents US 4843086, US 4886812 and patent applications WO 02/22590 A1 and WO 02/22591 A1. A procedure to these types of compound is also disclosed by C.S. Schneider and J. Mierau in J. Med. Chem., 1987, vol. 30, pages 494-498.

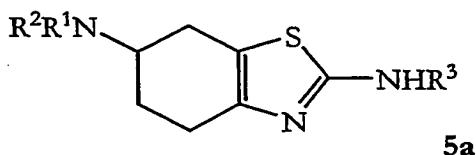
25

However, known processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are not satisfactory, particularly for industrial scale manufacture, as they have been found to be low yielding and involve the use of

hazardous and difficult to handle reagents such as bromine, hydrazine and potassium chromate.

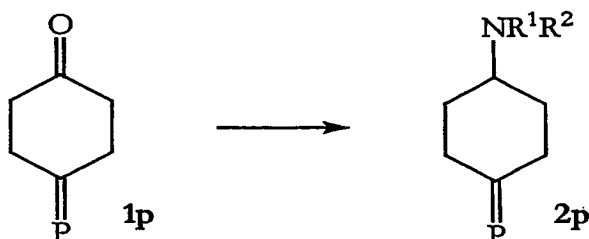
Summary of the invention

A first aspect of the present invention is a process for the preparation of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a



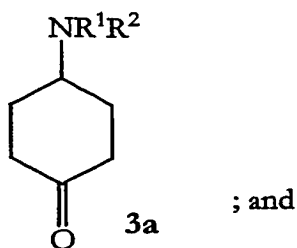
or a salt thereof, comprising the steps of:

- (a) reductively aminating a protected cyclohexandione **1p** with an amine R^1R^2NH to yield a protected 4-amino-cyclohexanone **2p**:



wherein P is a protected ketone functionality, and R^1 and R^2 are any atom or group or, together with the nitrogen to which they are attached, form a ring;

- (b) deprotecting the protected 4-amino-cyclohexanone **2p** to yield an unprotected 4-amino-cyclohexanone **3a**



- (c) treating the unprotected 4-amino-cyclohexanone **3a** with iodine and a substituted thiourea $H_2N(C=S)NHR^3$, wherein R^3 is any atom or group, to yield the 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof.

For the purposes of the present invention, an "alkyl" group is defined as a monovalent saturated hydrocarbon, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkyl groups are methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups. Preferably an alkyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkyl group is a C₁-C₁₂ alkyl group, which is defined as an alkyl group containing from 1 to 12 carbon atoms. More preferably an alkyl group is a C₁-C₆ alkyl group, which is defined as an alkyl group containing from 1 to 6 carbon atoms. An "alkylene" group is similarly defined as a divalent alkyl group.

An "alkenyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon double bond, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkenyl groups are vinyl, allyl, but-1-enyl and but-2-enyl groups. Preferably an alkenyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkenyl group is a C₂-C₁₂ alkenyl group, which is defined as an alkenyl group containing from 2 to 12 carbon atoms. More preferably an alkenyl group is a C₂-C₆ alkenyl group, which is defined as an alkenyl group containing from 2 to 6 carbon atoms. An "alkenylene" group is similarly defined as a divalent alkenyl group.

An "alkynyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon triple bond, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkynyl groups are ethynyl, propargyl, but-1-ynyl and but-2-ynyl groups. Preferably an alkynyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkynyl group is a C₂-C₁₂ alkynyl group, which is defined as an alkynyl group containing from 2 to 12 carbon atoms. More preferably an alkynyl group is a C₂-C₆ alkynyl group, which is defined as an alkynyl group containing from 2 to 6 carbon atoms. An "alkynylene" group is similarly defined as a divalent alkynyl group.

An "aryl" group is defined as a monovalent aromatic hydrocarbon. Examples of aryl groups are phenyl, naphthyl, anthracenyl and phenanthrenyl groups. Preferably

an aryl group does not include any heteroatoms in its carbon skeleton. Preferably an aryl group is a C₄-C₁₄ aryl group, which is defined as an aryl group containing from 4 to 14 carbon atoms. More preferably an aryl group is a C₆-C₁₀ aryl group, which is defined as an aryl group containing from 6 to 10 carbon atoms. An “arylene” group is similarly defined as a divalent aryl group.

Where a combination of groups is referred to as one moiety, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule. A typical example of an arylalkyl group is benzyl.

For the purposes of this invention, an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group may be substituted with one or more of -F, -Cl, -Br, -I, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -SH, -NH₂, -CN, -NO₂, -COOH, -R⁴-O-R⁵, -R⁴-S-R⁵, -R⁴-SO-R⁵, -R⁴-SO₂-R⁵, -R⁴-SO₂-OR⁵, -R⁴O-SO₂-R⁵, -R⁴-SO₂-N(R⁵)₂, -R⁴-NR⁵-SO₂-R⁵, -R⁴O-SO₂-OR⁵, -R⁴O-SO₂-N(R⁵)₂, -R⁴-NR⁵-SO₂-OR⁵, -R⁴-NR⁵-SO₂-N(R⁵)₂, -R⁴-N(R⁵)₂, -R⁴-N(R⁵)₃⁺, -R⁴-P(R⁵)₂, -R⁴-Si(R⁵)₃, -R⁴-CO-R⁵, -R⁴-CO-OR⁵, -R⁴O-CO-R⁵, -R⁴-CO-N(R⁵)₂, -R⁴-NR⁵-CO-R⁵, -R⁴O-CO-OR⁵, -R⁴O-CO-N(R⁵)₂, -R⁴-NR⁵-CO-OR⁵, -R⁴-NR⁵-CO-N(R⁵)₂, -R⁴-CS-R⁵, -R⁴-CS-OR⁵, -R⁴O-CS-R⁵, -R⁴-CS-N(R⁵)₂, -R⁴-NR⁵-CS-R⁵, -R⁴O-CS-OR⁵, -R⁴O-CS-N(R⁵)₂, -R⁴-NR⁵-CS-OR⁵, -R⁴-NR⁵-CS-N(R⁵)₂ or -R⁵. In this context, -R⁴- is independently a chemical bond, a C₁-C₁₀ alkylene, C₁-C₁₀ alkenylene or C₁-C₁₀ alkynylene group. -R⁵ is independently hydrogen, unsubstituted C₁-C₆ alkyl or unsubstituted C₆-C₁₀ aryl. Optional substituent(s) are not taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituent(s).

Any optional substituent may be protected. Suitable protecting groups for protecting optional substituents are known in the art, for example from “Protective Groups in Organic Synthesis” by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991).

For the purposes of this invention, a "salt" is any acid addition salt, preferably a pharmaceutically acceptable acid addition salt, including but not limited to a hydrohalogenic acid salt such as hydrofluoric, hydrochloric, hydrobromic and hydroiodic acid salt; an inorganic acid salt such as nitric, perchloric, sulfuric and phosphoric acid salt; an organic acid salt such as a sulfonic acid salt (for example methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, isethionic, benzenesulfonic, p-toluenesulfonic or camphorsulfonic acid salt), acetic, malic, fumaric, succinic, citric, tartaric, benzoic, gluconic, lactic, mandelic, mucic, pantoic, pantothenic, oxalic and maleic acid salt; and an aminoacid salt such as ornithinic, glutamic and aspartic acid salt. The acid addition salt may be a mono- or di-acid addition salt. A preferred salt is a di-hydrohalogenic, di-sulphuric, di-phosphoric or di-organic acid salt. A most preferred salt is a di-hydrochloric acid salt.

P is a protected ketone functionality. Suitable protecting groups are commonly known in the art, for example from Chapter 4 of "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991).

Preferably the protected ketone functionality P is an acyclic ketal or derivative 1q, a cyclic ketal or derivative 1r, 1s or 1t, or a hydrazone or oxime 1u, as shown in Figure 4. More preferably P is a cyclic ketal 1r, most preferably P is a monoethyleneketal 1, as shown in Figures 2 and 3.

R¹, R² and R³ can be any atom or group. Preferably R¹ and R² are not amine protecting groups. Amine protecting groups are commonly known in the art, for example from Chapter 7 of "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991). Most preferably one of R¹ and R² is hydrogen and the other of R¹ and R² is an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton. Such an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton, does not encompass carbonyl -CO-R groups, wherein R is any atom or group.

Optionally R^1 , R^2 and R^3 are independently hydrogen or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton.

Optionally R^1 , R^2 and R^3 are independently an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton, and which may be optionally substituted with one or more of -F, -Cl, -Br, -I, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -SH, -NH₂, -CN, -NO₂, -COOH, -R⁴-O-R⁵, -R⁴-S-R⁵, -R⁴-SO-R⁵, -R⁴-SO₂-R⁵, -R⁴-N(R⁵)₂, -R⁴-Si(R⁵)₃, -R⁴-CO-R⁵, -R⁴-CO-OR⁵, -R⁴O-CO-R⁵, -R⁴-CO-N(R⁵)₂, -R⁴-NR⁵-CO-R⁵, -R⁴-CS-R⁵ or -R⁵, wherein

-R⁴- is independently a chemical bond, a C₁-C₁₀ alkylene, C₁-C₁₀ alkenylene or C₁-C₁₀ alkynylene group, and

-R⁵ is independently hydrogen, unsubstituted C₁-C₆ alkyl or unsubstituted C₆-C₁₀ aryl.

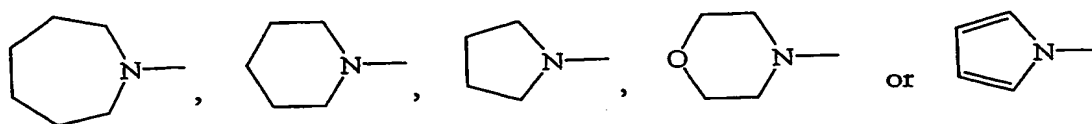
Optionally R^1 , R^2 and R^3 are independently an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which does not include any heteroatoms in its carbon skeleton, and which may be optionally substituted with one or more of -F, -Cl, -Br, -I, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -SH, -NH₂, -CN, -NO₂, -COOH, -OR⁵, -SR⁵, -SO-R⁵, -SO₂-R⁵, -N(R⁵)₂, -Si(R⁵)₃, -CO-R⁵, -CO-OR⁵, -O-CO-R⁵, -CO-N(R⁵)₂, -NR⁵-CO-R⁵, -CS-R⁵ or -R⁵, wherein

-R⁵ is independently hydrogen, unsubstituted C₁-C₆ alkyl or unsubstituted C₆-C₁₀ aryl.

Preferably R^1 , R^2 and R^3 are independently hydrogen or an unsubstituted alkyl, aryl or heteroaryl group, which does not include any heteroatoms N, O or S in its carbon skeleton. More preferably, R^1 , R^2 and R^3 are independently hydrogen or an unsubstituted C₁₋₁₀ alkyl group. More preferably, R^1 , R^2 and R^3 are independently hydrogen or an unsubstituted C₁₋₆ alkyl group. More preferably, one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an unsubstituted C₁₋₆ alkyl group, and R^3 is

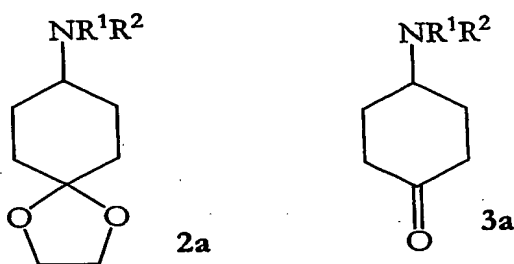
hydrogen. Most preferably, one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl, and R^3 is hydrogen.

Alternatively, R^1 and R^2 can, together with the nitrogen to which they are attached, form a ring. Optionally $-NR^1R^2$ together form an optionally substituted heterocycloalkyl, heterocycloalkenyl or heteroaryl ring. Optionally $-NR^1R^2$ together form



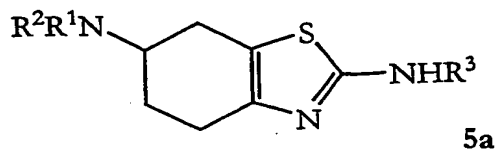
10 Preferably the reductive amination of step (a) is carried out with $NaCNBH_3$.

A second aspect of the present invention is a 4-amino-cyclohexanone-ethyleneketal 2a or a 4-amino-cyclohexanone 3a



15 for use in a process of the first aspect of the present invention. R^1 and R^2 are as defined above with reference to the first aspect of the present invention. Preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl.

20 A third aspect of the present invention is a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a



or a salt thereof, obtained by a process of the first aspect of the present invention. R^1 , R^2 and R^3 are as defined above with reference to the first aspect of the present

invention. Preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is n -propyl, and R^3 is hydrogen. Preferably the compound is a di-hydrochloric acid salt.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a or salts thereof have at least one chiral centre and can therefore exist in the form of various stereoisomers. The present invention embraces all of these stereoisomers and mixtures thereof. Mixtures of these stereoisomers can be resolved by conventional methods, for example, chiral chromatography, fractional recrystallisation, derivatisation to form diastereomers and subsequent resolution, and resolution using enzymes.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or salt thereof of the present invention preferably comprises at least 95% of the (R)- or the (S)-enantiomer, preferably at least 98% of the (R)- or the (S)-enantiomer, and more preferably at least 99% of the (R)- or the (S)-enantiomer. Generally, the (S)-enantiomer is the preferred enantiomer.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or salt thereof may be used as a medicament, preferably for the treatment of a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease.

A fourth aspect of the present invention is a pharmaceutical composition, comprising 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or salt thereof and a pharmaceutically acceptable carrier or diluent. Preferably the pharmaceutical composition is suitable for the treatment of a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease.

A fifth aspect of the present invention is a method of treating a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease, comprising administering a therapeutically effective amount of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or a salt thereof to a subject in need of such treatment.

Brief description of the drawings

Figure 1 is a schematic illustration of the process of the present invention.

Figures 2 and 3 are schematic illustrations of preferred processes of the present invention.

Figure 4 illustrates preferred protected ketone functionalities P.

Detailed description of the invention

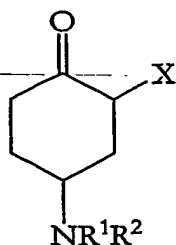
10 The inventors have found that processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a are greatly improved by the process outlined in Figure 1, wherein R^1 and R^2 can be any atom or group or, together with the nitrogen to which they are attached, form a ring, and wherein R^3 can be any atom or group. R^1 , R^2 and R^3 are preferably hydrogen or an unsubstituted alkyl, aryl or
15 heteroaryl group.

The process outlined in Figure 1 is short, utilises a readily available starting material, a protected cyclohexandione 1p, and does not require any hazardous chemical reagents. Each step of the process is high yielding and affords products of very
20 high purity.

Therefore a first aspect of the current invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a by the process specified in Figure 1.

25

It has been disclosed in prior art documents WO 02/22590 and WO 02/22591 that, in practice, compounds of formula 5a, comprising a primary amino or a secondary alkylamino group, cannot be prepared directly from the corresponding ketones 3a. The process shown in Figure 1, however, illustrates that the process of the current invention does indeed allow a compound 5a to be prepared from ketones 3a directly
30 without the requirement of preparing and isolating an α -haloketone of formula 4, where X is a halide such as chloride or bromide, or the requirement of a protecting group on the nitrogen atom of the amine substituent $-NR^1R^2$ of the ketone 3a.



Therefore, in a preferred embodiment of the present invention, the α -haloketone of formula 4 is not isolated. Moreover, in a preferred embodiment of the present invention, the nitrogen atom of the amine substituent $-NR^1R^2$ of the ketone 3a is not protected.

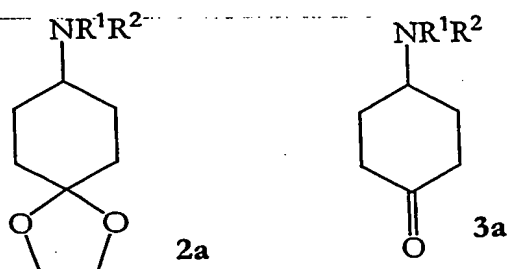
In a preferred embodiment of the first aspect of the invention, cyclohexandione is protected as a cyclohexandione monoethyleneketal 1, as shown in Figures 2 and 3.

A further preferred embodiment of the first aspect of the invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole 5, as outlined in Figure 3.

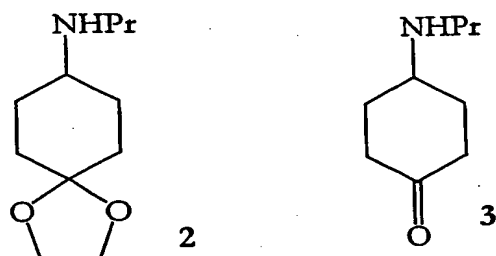
The process outlined in Figure 3 can readily be adapted to afford pramipexole I or its salts, for example by resolution of compound 5. Methods for resolving enantiomers are well known in the art and include, for example, chiral chromatography, fractional recrystallisation, derivatisation to form diastereomers and subsequent resolution, and resolution using enzymes.

A further aspect of the invention is therefore pramipexole I and its salts, when prepared by a process according to the current invention.

Further aspects of the invention include novel compounds of the formula 2a or 3a, wherein R^1 and R^2 are as defined above, which are useful intermediates in the synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a.



Preferred embodiments of these aspects are compounds 2 and 3, as shown in Figure 3.



The process outlined in Figure 3 is an example of a procedure comprising the process of the current invention and detailed procedures for this process are found in the experimental section. Compounds of the current invention are also exemplified in Figure 3 and in the experimental section.

The process of the present invention is short, utilises readily available starting materials and does not involve the use of hazardous or difficult to handle reagents such as bromine, hydrazine or potassium chromate. Each step of the process of the present invention is high yielding and affords products of very high purity. Thus the process is easy to scale up for industrial scale manufacturing. Optionally 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a and salts thereof may be manufactured in batches of 5kg or more, or even 10kg or more.

Experimental procedure

4-n-Propylamino-cyclohexanone-ethyleneketal 2

A mixture of *n*-propyl amine (162ml, 1.474mol) in methanol (500ml) was chilled to 0-5°C. To this solution was added methanolic hydrochloric acid (155ml, 44.47%) dropwise over a period of 30 minutes to achieve a pH of 6-7. Cyclohexandione monoethyleneketal 1 (100g, 0.641mol) was charged at 5°C and the reaction was stirred for 15 minutes. Sodium cyanoborohydride (60g, 0.952mol) was added in 15 minutes at 5°C. The pH increased to about 8 and methanolic hydrochloric acid (15ml, 44.47%) was added to bring the pH to 6-7. The reaction was allowed to come to 24-26°C. Stirring was continued for 2 hours. Methanol was distilled off (450ml). Sodium carbonate (95g, 0.896mol) was dissolved in water (850ml) and charged to the reaction mass at ambient temperature in one shot. The reaction mass was extracted with dichloromethane (2500ml). The dichloromethane layers were combined and dried over sodium sulfate (8.5g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product 2 was light yellow viscous oil. The weight of the product 2 obtained was 135g (105.8%); GC purity 97.74%.

¹H NMR (δ ppm): 0.9-1.0 (t, 3H, CH₃ of *n*Pr); 1.5-1.7 (m, 7H, CH₂CH₃ of *n*Pr and 5H of cyclohexyl ring); 1.75-1.85 (m, 2H, 2H of cyclohexyl ring); 1.95-2.05 (m, 1H, 1H of cyclohexyl ring); 2.75 (t, 2H, CH₂CH₂CH₃ of *n*Pr); 3.75-3.85 (m, 1H, NHCH); 3.9 (s, 2H, CH₂ of ethylene ketal) and 4.0 (s, 2H, CH₂ of ethylene ketal).

¹³C NMR (δ ppm): 11.7 (CH₃ of *n*Pr); 21.8 (CH₂CH₃ of *n*Pr); 28.5 (C-3 and C-5); 33.1 (C-2 and C-6); 48.3 (CH₂CH₂CH₃ of *n*Pr); 55.8 (C-4); 64.5 (C of ethylene ketal); 64.6 (C of ethylene ketal); 108.1 (C-1).

4-*n*-Propylamino-cyclohexanone 3

4-*N*-propylamino-cyclohexanone-ethyleneketal 2 (134g, 0.673mol) was taken in tetrahydrofuran (268ml) and cooled to 4-6°C. Concentrated hydrochloric acid (178ml, 2.01mol) was diluted with water (2144ml) and the mixture was cooled to 4°C. This diluted hydrochloric acid was added to the reaction mixture at 4-6°C in 15 minutes. The reaction was allowed to come to 24-26°C and stirring was continued for 24 hours. The reaction mass (2750ml) was concentrated to 1800ml at 50°C and 35mbar pressure. Sodium carbonate (148g, 1.4mol) was added to achieve

pH 10. The reaction mixture was extracted with dichloromethane (3670ml). The dichloromethane layers were combined and dried over sodium sulfate (20g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product 3 was yellow viscous oil. The weight of the product 3 obtained was 52.5g (52.84%); GC purity 86.07%.

¹H NMR (δ ppm): 0.9-1.0 (t, 3H, CH₃ of *n*Pr); (m, 2H, CH₂CH₃ of *n*Pr); 1.6-1.75 (m, 2H, 2H of cyclohexyl ring); 2.05-2.15 (m, 2H, 2H of cyclohexyl ring); 2.2-2.3 (m, 2H, 2H of cyclohexyl ring); 2.4-2.55 (m, 2H, 2H of cyclohexyl ring); 2.55-2.65 (t, 2H, CH₂CH₂CH₃ of *n*Pr); 2.9-3.0 (m, 1H, NHCH).
¹³C NMR (δ ppm): 12.3 (CH₃ of *n*Pr); 24.0 (CH₂CH₃ of *n*Pr); 32.6 (C-3 and C-5); 39.1 (C-2 and C-6); 50.0 (CH₂CH₂CH₃ of *n*Pr); 54.4 (C-4); 211.9 (C-1).

2-Amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole 5

4-*n*-Propylamino-cyclohexanone 3 (5g, 32.26mmol) was charged in absolute ethanol (50ml) at 24-26°C. Iodine (8.5g, 33.5mmol) was added to it under stirring followed by thiourea (5g, 65.7mmol) at 24-26°C. The reaction mass was refluxed for 32 hours. Heating was stopped and the reaction mass was allowed to cool to 24-26°C. It was maintained at that temperature for 20 hours. 2-Amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole dihydroiodide salt crystallized out of the solution. Ethanol (30ml) was distilled out on the rotavapor at 50°C and 100mbar. Acetone (50ml) was added and the solid was filtered. The solid was dried at 40°C and 15mbar. The weight of the product obtained was 8.5g (56%); HPLC purity 94.97%.

¹H NMR (δ ppm): 0.9-1.0 (t, 3H, CH₃ of *n*Pr) 1.6-1.8 (m, 2H, CH₂CH₃ of *n*Pr); 2.0 (m, 1H, H-7a); 2.35 (m, 1H, H-7b); 2.7 (m, 3H, H-5a, H-8a, H-8b); 3.1 (m, 3H, H-5b and CH₂CH₂CH₃ of *n*Pr); 3.7 (m, 1H, NHCH).
¹³C NMR (δ ppm): 12.0 (CH₃ of *n*Pr); 21.0 (CH₂CH₃ of *n*Pr); 22.2 (C-7); 25.5 and 26.8 (C-5 and C-8); 48.7 (CH₂CH₂CH₃ of *n*Pr); 54.7 (C-6); 113.0 (C-4); 134 (C-9); 171.2 (C-2).

Mass Spec: M⁺ 211 (expected 211).

The 2-amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole dihydroiodide salt formed above (50g, 107.1mmol) was dissolved in water (200ml). The solution was cooled to 4°C and solid sodium hydroxide (50g, 1.25mol) was added in 15 minutes. The reaction was stirred for 1 hour at 24-26°C and the solid that precipitated out
5 was filtered and dried at 40°C and 15mbar. The weight of the product 5 obtained was 17.07g (75.5%); HPLC purity 99.88%.

¹H NMR (δ ppm): 0.9-1.0 (t, 3H, CH₃ of *n*Pr); 1.5-1.6 (m, 2H, CH₂CH₃ of *n*Pr); 2.1 (m, 1H, H-7a); 2.3 (m, 1H, H-7b); 2.5-2.6 (m, 5H, H-5a, H-5b, H-8a, H-8b and
10 CHCH₂CH₃ of *n*Pr); 2.9 (m, 2H, H-6 and CHCH₂CH₃ of *n*Pr).

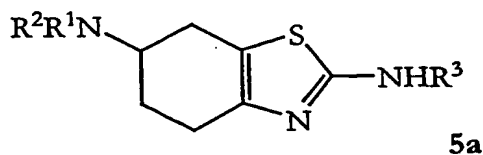
¹³C NMR (δ ppm): 12.0 (CH₃ of *n*Pr); 24.6 (CH₂CH₃ of *n*Pr); 26.6 (C-7); 30.7 and 30.9 (C-5 and C-8); 50.7 (CH₂CH₂CH₃ of *n*Pr); 56.2 (C-6); 116.0 (C-4); 145 (C-9); 170.4 (C-2).

Mass Spec: M⁺ 211 (expected 211).

15 It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope of the invention, which is defined by the following claims.

Claims

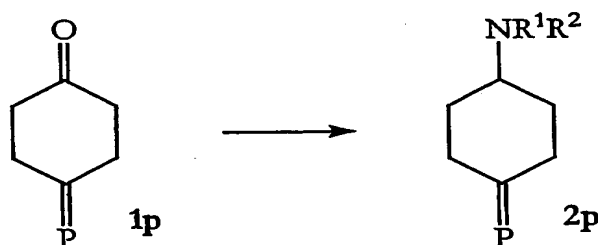
1. A process for the preparation of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a



5

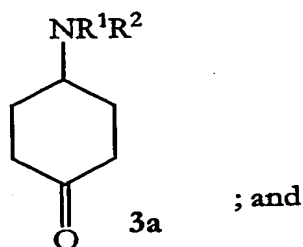
or a salt thereof, comprising the steps of:

(a) reductively aminating a protected cyclohexandione 1p with an amine R^1R^2NH to yield a protected 4-amino-cyclohexanone 2p:



10 wherein P is a protected ketone functionality, and R^1 and R^2 are any atom or group or, together with the nitrogen to which they are attached, form a ring;

(b) deprotecting the protected 4-amino-cyclohexanone 2p to yield an unprotected 4-amino-cyclohexanone 3a



15 (c) treating the unprotected 4-amino-cyclohexanone 3a with iodine and a substituted thiourea $H_2N(C=S)NHR^3$, wherein R^3 is any atom or group, to yield the 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or a salt thereof.

2. A process as claimed in claim 1, wherein P is a cyclic ketal 1r.

3. A process as claimed in claim 2, wherein P is a monoethyleneketal 1.

4. A process as claimed in any preceding claim, wherein R^1 , R^2 and R^3 are independently hydrogen or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton.

5. A process as claimed in any preceding claim, wherein R^1 , R^2 and R^3 are independently hydrogen or an unsubstituted alkyl, aryl or heteroaryl group, which does not include any heteroatoms N, O or S in its carbon skeleton.

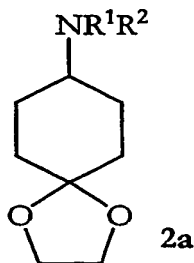
6. A process as claimed in any preceding claim, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton.

7. A process as claimed in claim 6, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl.

8. A process as claimed in any preceding claim, wherein R^3 is hydrogen.

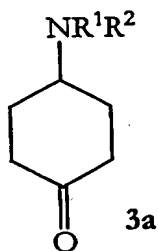
9. A process as claimed in any preceding claim, wherein the reductive amination of step (a) is carried out with NaCNBH_3 .

10. A 4-amino-cyclohexanone-ethyleneketal 2a



for use in a process as claimed in any one of claims 1 to 9.

11. A 4-amino-cyclohexanone 3a



for use in a process as claimed in any one of claims 1 to 9.

- 5 12. A compound as claimed in claim 10 or claim 11, wherein one of R¹ and R² is hydrogen and the other of R¹ and R² is *n*-propyl.

13. A 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or a salt thereof, obtained by a process as claimed in any one of claims 1 to 9.

10

14. A compound as claimed in claim 13, wherein one of R¹ and R² is hydrogen and the other of R¹ and R² is *n*-propyl, and wherein R³ is hydrogen.

- 15 15. A compound as claimed in claim 13 or claim 14, wherein the compound is a di-hydrochloric acid salt.

16. A compound as claimed in any one of claims 13 to 15, comprising at least 95% of the (R)- or the (S)-enantiomer.

- 20 17. A compound as claimed in any one of claims 13 to 16 for use as a medicament.

18. A compound as claimed in claim 17, wherein the medicament is suitable for the treatment of a psychiatric or neurological disorder.

25

19. A compound as claimed in claim 18, wherein the psychiatric or neurological disorder is schizophrenia, Alzheimer's disease or Parkinson's disease.

20. A pharmaceutical composition, comprising a compound as claimed in any one of claims 13 to 19 and a pharmaceutically acceptable carrier or diluent.

21. A pharmaceutical composition as claimed in claim 20, suitable for the
5 treatment of a psychiatric or neurological disorder.

22. A pharmaceutical composition as claimed in claim 21, wherein the psychiatric or neurological disorder is schizophrenia, Alzheimer's disease or Parkinson's disease.

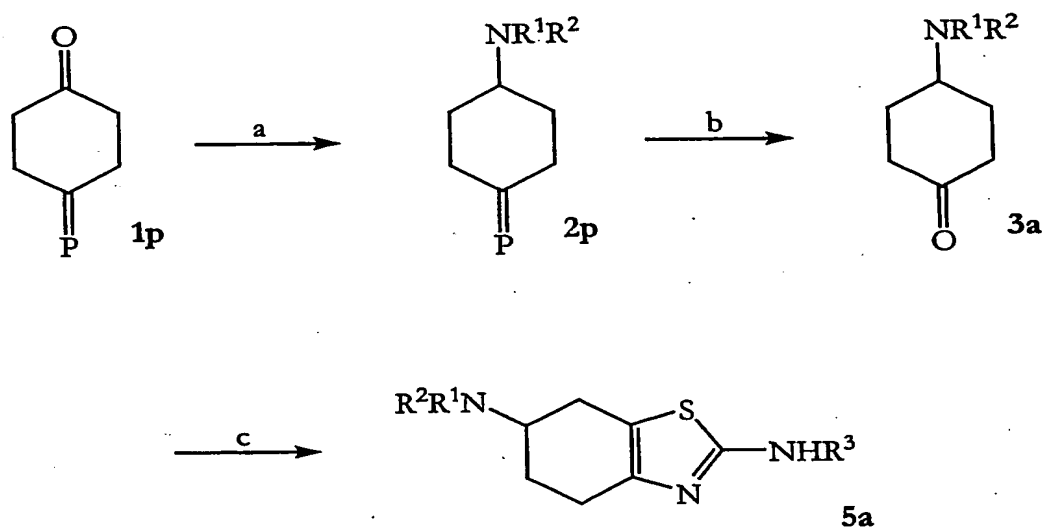
10

23. A method of treating a psychiatric or neurological disorder, comprising administering a therapeutically effective amount of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or a salt thereof as claimed in any one of claims 13 to 19 to a subject in need of such treatment.

15

24. A method as claimed in claim 23, wherein the psychiatric or neurological disorder is schizophrenia, Alzheimer's disease or Parkinson's disease.

20



a: reductive amination with R^1R^2NH

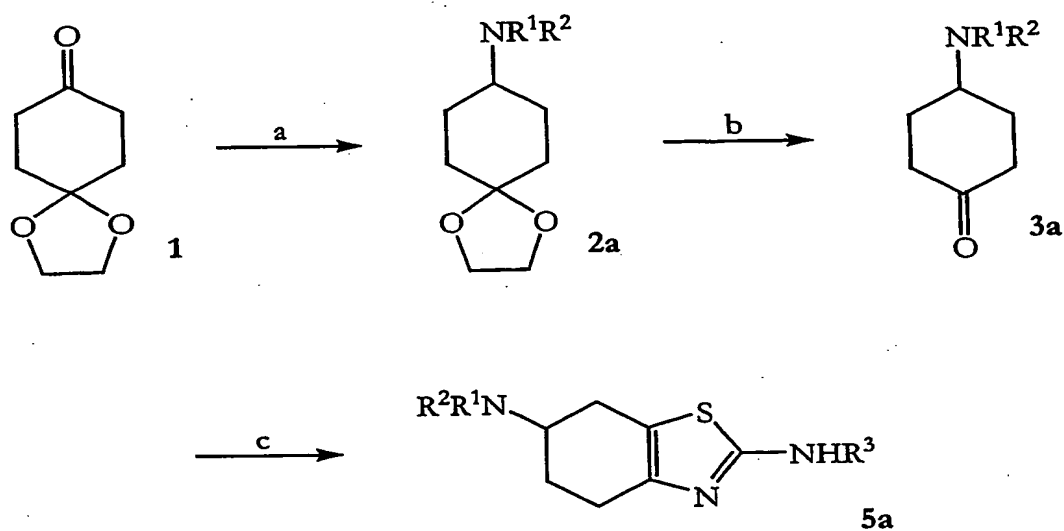
b: deprotection

c: (i) iodine, $H_2N(C=S)NHR^3$; (ii) OH^-

Figure 1

ORIGINAL FILED IN 11.5 MAR 2001

THIS PAGE BLANK (USPTO)



a: reductive amination with R^1R^2NH

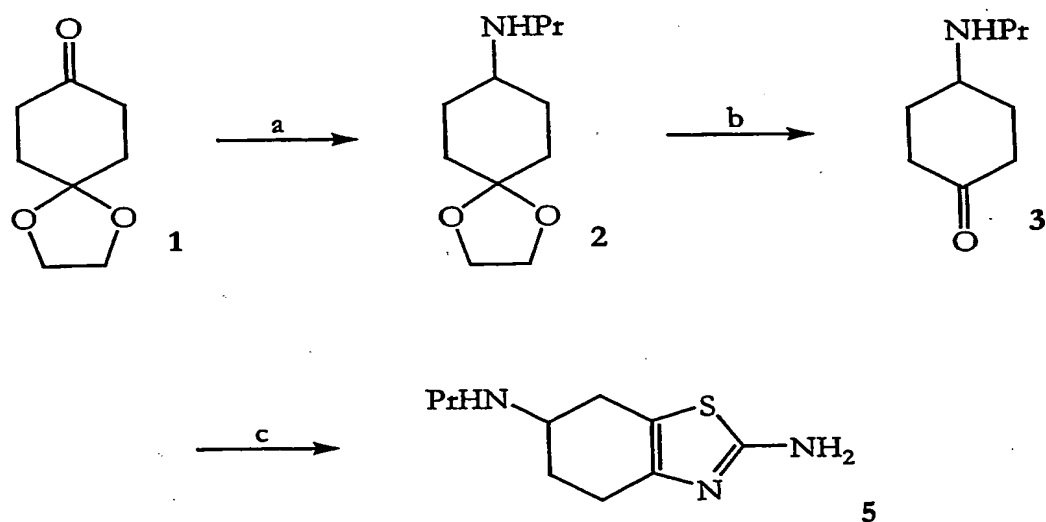
b: deprotection

c: (i) iodine, $H_2N(C=S)NHR^3$; (ii) OH^-

Figure 2

19.5 MAR 2003

THIS PAGE BLANK (USPTO)



a: *n*-propylamine, NaCNBH₃, MeOH/HCl

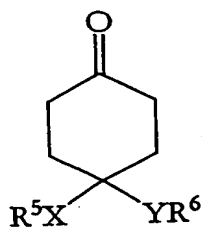
b: aq. HCl/THF

c: (i) iodine, H₂N(C=S)NH₂, ethanol, reflux; (ii) aq. NaOH

Figure 3

DT15 Rec'd PCT/PTO 15 MAR 2005

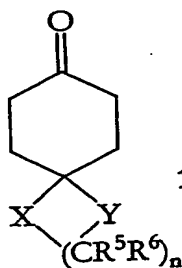
THIS PAGE BLANK (USPTO



1q

 $X, Y = O, S \text{ or } Se$

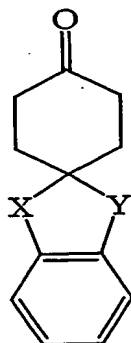
$R^5, R^6 = CO-R^7, Si(R^7)_3$, or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton

 $R^7 = \text{hydrogen or alkyl}$ and/or $XR^5, YR^6 = CN$ 

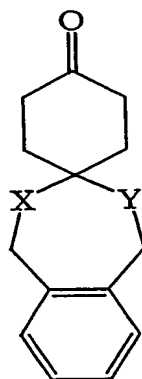
1r

 $X, Y = O, S, NR^7 \text{ or } Se$
 $n = 2 \text{ or } 3$

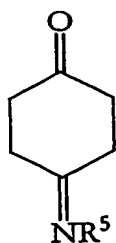
$R^5, R^6 = \text{hydrogen, halide, or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton}$

 $R^7 = \text{hydrogen or alkyl}$ 

1s

 $X, Y = O, S \text{ or } NR^6$
 $R^6 = \text{hydrogen or alkyl}$ 

1t

 $X, Y = O, S \text{ or } NR^6$
 $R^6 = \text{hydrogen or alkyl}$ 

1u

 $R^5 = N(R^6)_2 \text{ or } OR^6$

$R^6 = \text{hydrogen, or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton}$

Figure 4

DT15 Rec'd PCT/PTO . 1 5 MAR 2005

THIS PAGE BLANK (USPTO)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 03/04022

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/82 C07D317/72 C07C225/20 A61K31/429 A61P25/18
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 207 696 A (LILLY CO ELI) 7 January 1987 (1987-01-07) page 7, line 16 -page 9, line 2; claims 1-6	10,11,13
A	page 7, line 16 -page 11, line 4 page 16, line 10 -page 18, line 15 claims 1-12	1-24
X	WO 02 22590 A (POSPISILIK KAREL; LEMMENS JACOBUS MARIA (NL); SYNTHON B V (NL); HO) 21 March 2002 (2002-03-21) claims 9-18,20-22	13-16
A	page 19, line 5 -page 2, line 17; claims 9-18,20-22	1-24
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

10 February 2004

Date of mailing of the international search report

18/02/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

Inte

Application No

PCT/GB 03/04022

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 731 374 A (KOBINGER WALTER ET AL) 15 March 1988 (1988-03-15) cited in the application column 16, line 63 -column 17, line 3; claims	13,14, 17-24
A	column 3, line 34 -column 4, line 26 & US 4 886 812 A 12 December 1989 (1989-12-12) cited in the application & US 4 843 086 A cited in the application	1
X	WO 02 22591 A (POSPISILIK KAREL; SYNTHON B V (NL)) 21 March 2002 (2002-03-21) cited in the application page 1, line 5 -page 2, line 2 page 14, line 15 - line 29 page 17, line 20 - line 25	13-24
X	WO 96 18395 A (BOEHRINGER INGELHEIM KG; ROHDE FRANK A (DE); UPJOHN CO (US); HALL) 20 June 1996 (1996-06-20) claims	13-24
X	WO 99 59563 A (GOMEZ MANCILLA BALTAZAR; UPJOHN CO (US)) 25 November 1999 (1999-11-25) page 5, line 6 - line 18	13-15, 17-24
X	DE 36 20 813 A (BOEHRINGER INGELHEIM KG) 23 December 1987 (1987-12-23) claims 1,7,8; example 1	13,15-24
X	EP 0 749 962 A (LILLY CO ELI) 27 December 1996 (1996-12-27) page 14, line 17 - line 35 page 14, line 17 - line 38	10,11
A		1
X	US 5 708 187 A (FLAUGH MICHAEL EDWARD ET AL) 13 January 1998 (1998-01-13) column 17, line 53 -column 18, line 12 column 17, line 53 -column 18, line 18	10,11
A		1
X	EP 1 008 592 A (FUJIREBIO KK) 14 June 2000 (2000-06-14) example 118	10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-16

Process for the preparation of compound 5a, which is already known from the art, from intermediates 2a and 3a, these intermediates, and the known product 5a per se.

2. Claims: 17-24

Pharmaceutical compositions and methods making use of the known compound 5a.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/04022

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 23 and 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal

Application No

PCT/GB 03/04022

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0207696	A	07-01-1987	AU 5919586 A	08-01-1987
			EP 0207696 A1	07-01-1987
			JP 62000473 A	06-01-1987
			ZA 8604626 A	24-02-1988
WO 0222590	A	21-03-2002	ES 2187249 A1	16-05-2003
			AU 1105502 A	26-03-2002
			AU 1281502 A	26-03-2002
			EP 1318986 A1	18-06-2003
			WO 0222590 A1	21-03-2002
			WO 0222591 A1	21-03-2002
			US 2002103240 A1	01-08-2002
US 4731374	A	15-03-1988	DE 3447075 A1	03-07-1986
			DE 3508947 A1	18-09-1986
			AT 45735 T	15-09-1989
			AU 583874 B2	11-05-1989
			AU 5154485 A	17-07-1986
			BG 62023 B2	30-12-1998
			BR 1100678 A3	13-10-1999
			CA 1263653 A1	05-12-1989
			CS 9104099 A3	16-09-1992
			DD 242230 A5	21-01-1987
			DE 3572485 D1	28-09-1989
			DK 590285 A	23-06-1986
			EP 0186087 A1	02-07-1986
			ES 8702787 A1	01-04-1987
			ES 8707513 A1	16-10-1987
			ES 8707514 A1	16-10-1987
			ES 8707515 A1	16-10-1987
			FI 855102 A , B,	23-06-1986
			GR 853126 A1	22-04-1986
			HK 78692 A	23-10-1992
			HU 39736 A2	29-10-1986
			IE 58863 B1	17-11-1993
			IL 77415 A	19-03-1990
			JP 1854941 C	07-07-1994
			JP 5072907 B	13-10-1993
			JP 61155377 A	15-07-1986
			KR 9309791 B1	11-10-1993
			LU 90208 A9	06-04-1998
			MX 9202792 A1	30-06-1992
			NO 855195 A , B,	23-06-1986
			NZ 214661 A	26-04-1990
			PH 24533 A	03-08-1990
			PT 81735 A , B	01-01-1986
			SG 82492 G	04-12-1992
			US 4843086 A	27-06-1989
			US 4886812 A	12-12-1989
			ZA 8509731 A	26-08-1987
WO 0222591	A	21-03-2002	ES 2187249 A1	16-05-2003
			AU 1105502 A	26-03-2002
			AU 1281502 A	26-03-2002
			EP 1318986 A1	18-06-2003
			WO 0222590 A1	21-03-2002
			WO 0222591 A1	21-03-2002
			US 2002103240 A1	01-08-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: Application No

PCT/GB 03/04022

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9618395	A	20-06-1996	US 5650420 A AT 238790 T AU 712666 B2 AU 4413496 A CA 2207323 A1 DE 69530606 D1 DK 797439 T3 EP 0797439 A1 JP 10510809 T NZ 298606 A SI 797439 T1 WO 9618395 A1 US 6156777 A US 6458820 B1	22-07-1997 15-05-2003 11-11-1999 03-07-1996 20-06-1996 05-06-2003 25-08-2003 01-10-1997 20-10-1998 23-02-2001 31-12-2003 20-06-1996 05-12-2000 01-10-2002
WO 9959563	A	25-11-1999	AU 748629 B2 AU 3741999 A BR 9909917 A CA 2327299 A1 CN 1301159 T EP 1076559 A2 HU 0101803 A2 JP 2002515425 T NO 20005757 A PL 344574 A1 SK 16272000 A3 TR 200003356 T2 WO 9959563 A2 US 6503920 B1 ZA 200005847 A	06-06-2002 06-12-1999 26-12-2000 25-11-1999 27-06-2001 21-02-2001 28-03-2002 28-05-2002 14-11-2000 05-11-2001 10-05-2001 21-03-2001 25-11-1999 07-01-2003 19-04-2002
DE 3620813	A	23-12-1987	DE 3620813 A1 AT 70060 T AU 593357 B2 AU 7457887 A CA 1322372 C CS 8704511 A3 DD 259623 A5 DE 3774942 D1 DK 168437 B1 EP 0251077 A1 ES 2040226 T3 FI 872719 A ,B, GR 3003656 T3 HU 47091 A2 IE 60676 B1 JP 63017872 A KR 9504000 B1 NO 872574 A ,B, NZ 220800 A PH 24207 A PL 266361 A1 PT 85100 A ,B SU 1494867 A3 US 4981862 A ZA 8704470 A	23-12-1987 15-12-1991 08-02-1990 24-12-1987 21-09-1993 13-05-1992 31-08-1988 16-01-1992 28-03-1994 07-01-1988 16-10-1993 22-12-1987 16-03-1993 30-01-1989 10-08-1994 25-01-1988 22-04-1995 22-12-1987 21-12-1989 10-04-1990 13-10-1988 01-07-1988 15-07-1989 01-01-1991 22-02-1989
EP 0749962	A	27-12-1996	CA 2179678 A1	24-12-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No

PCT/GB 03/04022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0749962	A	DE 69610793 D1	07-12-2000
		DE 69610793 T2	03-05-2001
		EP 0749962 A1	27-12-1996
		ES 2151993 T3	16-01-2001
US 5708187	A	13-01-1998	US 5814653 A
			29-09-1998
EP 1008592	A	14-06-2000	EP 1008592 A2
			14-06-2000
		JP 2000204071 A	25-07-2000
		KR 2000035402 A	26-06-2000
		US 6117870 A	12-09-2000

THIS PAGE BLANK (USPTO)